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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

SWITZER, JULIET CAROLINE

ART UNIT PAPER NUMBER

1634

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/856,470

Applicant(s)

HAGBERG ET AL.

Examiner

Juliet C. Switzer

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12/22/03; 11/20/03.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2 and 4-6 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2, 4-6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/20/03 and 12/22/03 have been entered.
2. This action is written in response to applicant's correspondence submitted 11/20/03 and 12/22/03. The paper filed 11/20/03 contained only arguments which were addressed in an advisory action, but are addressed again herein. The paper filed 12/22/03 reiterated claims 2 and 4 and added claims 5 and 6. Claims 2 and 4-6 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112- New Matter

3. Claims 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims,

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the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "50 to 500 days" in claims 5 and 6 appears to represent new matter. Applicant's correspondence pointed to page 4, lines 6-10 of the specification as basis for this limitation. However, this portion of the specification fails to provide basis for the upper limit of 500 days. Since no basis has been identified, the claims are rejected as incorporating new matter.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2 and 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 4-6 are indefinite over the recitation of "having a "12" genotype" and "having a "11" genotype," respectively. The specification does not define these annotations to describe what a "11" genotype or a "12" genotype is, and thus, the method is unclear. The specification, at page 7 describes methods for the genotyping of the second exon of the myostatin gene, but the specification does not describe how this method relates to the designations "11" and "12." Thus, it is impossible to ascertain what genotype is being identified in claims 2 and 4-6.

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6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2 and 4-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 2 is drawn to a method of improving cholesterol levels in a subject in need of such improvement by identifying a subject with hypercholesteremia having a “12” genotype for a myostatin exon 2 gene and engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject. Claim 5 depends from claim 2 and further defines extensive exercise training as at least 10 single courses of exercise over an exercise period of from about 50 to 500 days.

Claim 4 is drawn to a method for improving diabetes status in a subject by identifying a subject with diabetes having a “11” genotype for a myostatin exon 2 gene and engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject. Claim 6 depends from claim 4 and further defines extensive exercise training as at least 10 single courses of exercise over an exercise period of from about 50 to 500 days.

As a first point, as noted in the rejections under 112 2nd paragraph, neither the specification nor the claims clearly set forth the meaning of the “11” or “12” genotypes, and thus, the methods of the instantly rejected claims are largely undefined. However, even if these

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genotypes were clearly defined, the specification is not enabling for the practice of the claimed methods.

The claimed methods both rely on the establishment of a relationship between particular alleles in the second exon of the myostatin gene and a particular phenotype (i.e. the ability to improve cholesterol levels with extensive exercise or the ability to improve diabetes status with extensive exercise). The prior art is silent with respect to polymorphisms in the human myostatin gene. However, the state of the art with regard to the establishment of such a relationship between a polymorphism and a phenotype is highly unpredictable. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β -globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Further, Ferrell *et al.* in a 1999 paper were unable to establish a relationship between a polymorphism in exon 2 of the myostatin gene (K153R) and muscle mass response to strength training. This paper is published after the filing of the provisional applications from which this application depends, but

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nonetheless highlights the unpredictability of establishing a relationship between even this particular myostatin polymorphism and a phenotype.

The data in the specification further highlight this unpredictability. With regard to methods for improving cholesterol status, the specification and claims assert that patients with a “12” genotype exhibit greater improvements after an extensive exercise routine for nine months. However, the data to support this assertion only represent three people total with the “12” genotype and the standard deviations in the data points given are nearly as large as the average values reported. No statistical analysis is provided, so it is unknown from the data whether a statistically significant correlation was observed. Certainly the ranges of improvement observed for patients with the “12” genotype versus the “11” genotype overlap when the standard deviations are considered. Thus, the data themselves demonstrate that it is not predictable, even once a genotype is observed which patients will exhibit an improvement even after nine months of an extensive exercise regime.

The data regarding an improvement in diabetes status also is widely variant and represents a small sample population. Again, no statistical analysis is presented to aid in the interpretation of the data. In light of these factors it is impossible to ascertain whether a reliable association has been demonstrated between nine months of an extensive exercise regime and an improvement in diabetes status correlated with a particular phenotype.

Furthermore, it is noted that the claims encompass “extensive exercise” for any length of time, yet the specification provides only a demonstration of the changes that occur after nine months of endurance exercise training. Claims 5 and 6 require that the “extensive exercise” is at least 10 single courses of exercise over a period from about 10 to about 500 days. However, the

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examples in the specification only demonstrate any sort of improvement over a nine month period of time for which any putative relationship is established in the specification is over 9 months- which is much greater than most of the range specifically encompassed by the claims. It is highly unpredictable as to what other shorter lengths of training would be sufficient to improve cholesterol or diabetes status for patients having the "12" or "11" genotypes, as appropriate.

Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability, the lack of clearly defined and analyzed working examples, and the breadth of the claims, it is concluded that undue experimentation would be required to practice the claimed invention.

Response to Remarks

In the arguments filed 11/20/03, Applicant sets forth that the recitation "having a "12" genotype" in claim 2 and having a "11" genotype in claim 4 would be readily understood by one of ordinary skill in the art. Applicant's own arguments in the prosecution history of this application highlight the fact that this language is not clear, as in two different papers, applicant set forth two different definitions for the "12" haplotype. In the previously filed arguments (see paper filed 4/7/03) applicant set forth that "It is further submitted that it would be understood by one of ordinary skill that the "11" genotype would contain Lys at position 153 and that "12" would contain arginine based upon the teachings of page 7, line 11 of the present specification." In the response filed 11/20/03 applicant sets forth that "12" refers to an AG genotype in terms of nucleotides and a lysine/artinine in terms of amino acids. The specification is silent as to the meaning of these identifiers. Even if the "12" genotype were established to be referring to a heterozygote (as set forth in present remarks), the specification still does not teach what the "11"

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genotype refers to. There are three possible genotypes at the locus- two different homozygous genotypes and one heterozygous genotype. The specification never sets forth which of these genotypes is being referred to using the codes "11" and "12." The section of the specification cited by applicant describes a method for genotyping but does not name the possible alleles or provide a definition of the identifiers. Thus, it is maintained that the claims are indefinite because it is not known which alleles are being referred to using the codes "11" and "12." The specification simply does not define these arbitrary codes.

With regard to the "extensive exercise" portion of the 112 1st paragraph rejection, applicant points out that the specification discusses a number of possible regimes that are considered "extensive exercise." Claims 5 and 6 have been added which specify a time period for exercise. However, some of these encompass periods of time that are much shorter than the nine months of the example, and there is no evidence in the specification that these shorter periods of time might be associated with improvement. Further, it is noted that applicant's arguments address only a small part of the enablement rejection, and even if these overcame the problem with the scope of "extensive exercise" the enablement rejection would still be maintained for the reasons of record.

Conclusion

8. No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.



Juliet C Switzer
Examiner
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January 26, 2004